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Opinion

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Application of Monoclonal Antibodies in Cancer Treatment

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Abstract

Monoclonal antibody-based immunotherapy has evolved into a pivotal component of cancer treatment, standing alongside surgery, radiation, and chemotherapy. With a diverse array of clinically relevant mechanisms of action, monoclonal antibodies not only directly target tumor cells but also stimulate enduring anti-tumor immune responses. The multifaceted properties of antibodies as a therapeutic platform have spurred the development of novel cancer treatment strategies, significantly impacting cancer care. This review delves into the established mechanisms of action, current clinical applications for cancer treatment, and the mechanisms of resistance associated with monoclonal antibody therapy. Additionally, it explores the shift in monoclonal antibody-based strategies towards augmenting anti-tumor immune responses by targeting immune cells rather than solely focusing on tumor antigens, along with an examination of ongoing combination therapies.

Keywords: Monoclonal antibody; Cancer; Immunology

Introduction

Behring and Shibasaburo, in their work on animal models of diphtheria in 1890, initially characterized antibodies as neutralizing substances present in the blood. Subsequent to this discovery, a series of significant scientific breakthroughs over the ensuing century laid the foundation for the utilization of antibodies as a therapeutic option for cancer. Heidelberger and Avery identified antibodies as proteins capable of recognizing specific antigens, while in 1947, Astrid Fagraeus demonstrated that plasma B cells from the adaptive immune system were responsible for producing antibodies.Following the advent of hybridomas, exploration into the application of mAbs for cancer treatment commenced. Anti-melanoma mAbs demonstrated the ability to inhibit the growth of human melanomas in nude mice. In 1980, a milestone was achieved with the initiation of the first human trial employing mAb therapy against cancer, specifically in a lymphoma patient. Regrettably, early therapeutic monoclonal antibodies, due to their murine origins, proved immunogenic in humans and were ineffective inducers of immunity in patients. This limitation significantly restricted their clinical utility. In the late 1980s, breakthrough techniques emerged to humanize antibodies, aiming to overcome these challenge.

Continued progress has led to the creation of "fully-human" antibodies through the use of transgenic mice or in vitro systems like yeast or phage display. These advancements in antibody engineering have positioned Monoclonal Antibodies (mAbs) as a significant modality in cancer treatment. What sets antibodies apart is their unique capacity to not only directly eliminate tumor cells but also to engage the host immune system, fostering enduring effector responses against the tumor. The amalgamation of a multifaceted mechanism of action with target specificity distinguishes mAb therapy from conventional treatments like chemotherapy. This underpins the ability of antibodies to evoke potent anti-tumor responses while mitigating the risk of toxicity and adverse events.

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Structure of Antibodies

Antibodies, belonging to the Immunoglobulin (Ig) superfamily, are sizable glycoproteins crucial to the immune system's function. Their primary role involves recognizing foreign antigens, neutralizing them, and triggering subsequent immune responses. Structurally, antibodies consist of two heavy and two light chains forming a Y shape. Each tip of the Y contains the Fragment Antigen-Binding (Fab) portion, responsible for specific antigen recognition. The Fragment Crystallizable (Fc) region, located at the Y's base, facilitates interactions between the antibody and other immune system components. Fc regions of antibodies are acknowledged by Fc Receptors (FcRs) present on various immune cells. Classified into five distinct classes—IgA, IgD, IgE, IgG, and IgM—based on their heavy chains, antibodies play diverse roles. IgG, the most frequently used form in antibody therapy, interacts with its associated Fc receptor, FcγR. This receptor is found on Natural Killer (NK) cells, neutrophils, monocytes, dendritic cells, and eosinophils, enabling specialized functions like Antibody-Dependent Cellular Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC). Within the IgG class, further subdivision occurs based on the Fc region's ability to facilitate these functions: IgG1 and IgG3 can elicit ADCC and CDC, whereas IgG2 and IgG4 cannot.

Monoclonal antibodies, on the other hand, are clonal versions of specific antibody isotypes, precisely targeted to a unique antigen epitope.

Monoclonal Antibodies (mAbs) designed to target antigens specific to tumor cells or those overexpressed by them can trigger tumor cell death through various mechanisms. One primary direct mechanism involves the obstruction of growth factor receptor signaling. The signaling promoting tumor growth and survival is disrupted as mAbs bind to their target growth factor receptors, altering their activation state or preventing ligand binding. For instance, the Epidermal Growth Factor Receptor (EGFR), overexpressed in numerous cancers, initiates tumor cell proliferation, migration, and invasion through its signaling pathway. Cetuximab, an anti-EGFR mAb, induces apoptosis in tumor cells by obstructing ligand binding and receptor dimerization. Another example is the Human Epidermal

Growth Factor Receptor 2 (HER2), a tyrosine kinase receptor overexpressed in various cancers, particularly ovarian and breast carcinomas. Unlike EGFR, HER2 lacks a known ligand and instead forms heterodimers with other growth factor receptors to amplify their activation.

Clinical Use

Over the last three decades, a variety of treatments derived from Monoclonal Antibodies (mAbs) have been clinically employed, aiming to harness the potential of targeted therapy. Antibodies serve as highly adaptable platforms for the development of innovative therapeutics, resulting in a broad spectrum of approaches. The identification of tumor-specific antigens suitable for targeting has sparked interest in the design of immunotherapies. With the advent of monoclonal antibodies, there was anticipation that using them to target tumor cell antigens could offer a more effective and less toxic alternative to traditional chemotherapy. In 1988, scientists identified CD20, a protein specifically associated with mature B cells. CD20 was observed to be abundantly expressed on cancerous B cells in non-Hodgkin's lymphoma, distinguishing it from healthy immature B cells. Consequently, a Monoclonal Antibody (mAb) treatment directed at CD20 could effectively eliminate cancerous cells, leaving immature B cells untouched to replenish the pool of healthy cells. CD20 thus emerged as the inaugural target for mAb therapy, with the anti-CD20 mAb rituximab securing the distinction of being the first monoclonal antibody approved for cancer treatment. The success of targeting antigens overexpressed on solid tumor cells has led to the identification of numerous monoclonal antibodies demonstrating efficacy as cancer therapeutics.

Combination Therapies

While Monoclonal Antibodies (mAb) have demonstrated success as monotherapy in certain patients, the current trend in treatment paradigms leans toward utilizing them in combinations with chemotherapy, radiation, molecularly targeted drugs like tyrosine kinase inhibitors, other antibodies targeting the same antigen, immune checkpoint inhibitors, vaccines, and/or cellular therapies. Numerous combination strategies are currently undergoing both preclinical investigation and clinical trials, with this expansive field extensively covered elsewhere. While there are numerous immune checkpoints regulating T-cell activation, each checkpoint operates through distinct mechanisms. Consequently, combinations of Immune Checkpoint Blockade (ICB) targeting multiple checkpoints are anticipated to enhance T cell responses synergistically. In preclinical mouse models, the combination of Monoclonal Antibodies (mAbs) targeting CTLA-4 and PD-1 exhibited significantly improved efficacy compared to either antibody alone. Similarly, in patients with metastatic melanoma, combined therapy utilizing ipilimumab and nivolumab demonstrated superior effectiveness than either treatment used as a monotherapy. Following this success, the FDA has approved the combination of ipilimumab and nivolumab for melanoma treatment. As the first ICB combination with FDA approval, ongoing clinical trials are actively assessing the efficacy of ipilimumab plus nivolumab in various other cancer types.

Conclusion

Monoclonal Antibody (mAb) therapy has recently emerged as a prominent modality for cancer treatment, but many aspects of its mechanisms of action and clinical relevance remain poorly understood. Despite notable clinical successes, therapeutic resistance poses a significant challenge. Future studies should prioritize the analysis of mAb mechanisms of action to unveil new approaches for enhancing clinical efficacy. For example, research has indicated that Antibody-Dependent Cellular Cytotoxicity (ADCC) plays a crucial role in mediating mAb responses, making engineering strategies to augment ADCC activity a promising avenue.

Combining tumor-targeted mAbs with Immune Checkpoint Blockade (ICB) has demonstrated several encouraging avenues for maximizing the clinical benefits of mAb therapy. Furthermore, mutations in both the antibody target and associated signaling pathways serve as important biomarkers of mAb efficacy and resistance. Future mAb treatment strategies should incorporate inhibitors of these alternative signaling pathways to counteract resistance. Ongoing research in these directions is essential for advancing the understanding and effectiveness of monoclonal antibody therapy in cancer treatment.

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